

WHAT IS CLAIMED IS:

1. A purified vertebrate Delta protein.
- 5 2. The protein of claim 1<sup>1</sup> which is a human protein.
3. The protein of claim 1<sup>1</sup> which is a mammalian protein.
- 10 4. The protein of claim 1<sup>1</sup> which comprises the amino acid sequence substantially as set forth in amino acid numbers 1-722 of SEQ ID NO:12.
- 15 5. A purified derivative or analog of the protein of claim 1<sup>1</sup>, which is able to display one or more functional activities of a Delta protein.
- 20 6. A purified derivative or analog of the protein of claim 2<sup>1</sup>, which is able to display one or more functional activities of a human or *D. melanogaster* Delta protein.
- 25 7. The derivative or analog of claim 5<sup>1</sup> which is able to be bound by an antibody directed against a human or *D. melanogaster* Delta protein.
8. A purified fragment of the protein of claim 2<sup>1</sup>, which is able to be bound by an antibody directed against a human Delta protein.
- 30 9. A molecule comprising the fragment of claim 8<sup>1</sup>.
10. A purified fragment of the protein of claim 2<sup>1</sup> which is able to display one or more functional activities of a human Delta protein.
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11. A purified fragment of a vertebrate Delta protein comprising a domain of the protein selected from the group consisting of the extracellular domain, DSL domain, domain amino-terminal to the DSL domain, epidermal growth factor-like repeat domain, transmembrane domain, and intracellular domain.
12. A purified fragment of a Delta protein comprising the membrane-associated region of the protein.
13. A purified fragment of a Delta protein comprising an epidermal growth factor-homologous repeat of the protein.
14. The fragment of claim 11 in which the Delta protein is a human Delta protein.
15. A purified fragment of a vertebrate Delta protein comprising a region homologous to a Notch protein or a Delta protein, and consisting of at least six amino acids.
16. A purified fragment of a vertebrate Delta protein comprising the region of the protein with the greatest homology over an identical number of amino acids to amino acid numbers 1-722 as shown in Figure 8 (SEQ ID NO:12).
17. A chimeric protein comprising a fragment of a vertebrate Delta protein consisting of at least 20 amino acids fused via a covalent bond to an amino acid sequence of a second protein, in which the second protein is not the Delta protein.
18. The chimeric protein of claim 17 in which the fragment of a vertebrate Delta protein is a fragment capable of being bound by an anti-Delta antibody.

19. The chimeric protein of claim 18<sup>r</sup> in which the Delta protein is a human protein.

20. The chimeric protein of claim 19<sup>r</sup> which is able to display one or more functional activities of a Delta protein.

21. A purified fragment of a vertebrate Delta protein which (a) is capable of being bound by an anti-Delta antibody; and (b) lacks the transmembrane and intracellular domains of the protein.

22. A purified fragment of a vertebrate Delta protein which (a) is capable of being bound by an anti-Delta antibody; and (b) lacks the extracellular domain of the protein.

23. A purified fragment of a vertebrate Delta protein which is able to bind to a Notch protein.

24. The fragment of claim 23, which lacks the epidermal growth factor-like repeats of the Delta protein.

25. The fragment of claim 23 in which the Delta protein is a human Delta protein.

26. The fragment of claim 23, which is a fragment of SEQ ID NO:18.

27. A molecule comprising the fragment of claim 23.

28. The fragment of claim 11 or 21 in which the Delta protein is a human Delta protein.

29. An antibody which is capable of binding the Delta protein of claim 1, and which does not bind to a *Drosophila* Delta protein.

5 30. An antibody which is capable of binding the Delta protein of claim 2, and which does not bind to a *Drosophila* Delta protein.

10 31. The antibody of claim 1 which is monoclonal.

32. A molecule comprising a fragment of the antibody of claim 31, which fragment is capable of binding a Delta protein.

15 33. An isolated nucleic acid comprising a nucleotide sequence encoding a vertebrate Delta protein.

34. The nucleic acid of claim 33 which is DNA.

20 35. An isolated nucleic acid comprising a nucleotide sequence complementary to the nucleotide sequence of claim 33.

25 36. An isolated nucleic acid comprising a nucleotide sequence encoding the Delta protein of claim 2.

37. An isolated nucleic acid comprising a fragment of a vertebrate Delta gene consisting of at least 50 nucleotides.

30 38. An isolated nucleic acid comprising a nucleotide sequence encoding the fragment of claim 10.

35 39. An isolated nucleic acid comprising a nucleotide sequence encoding the fragment of claim 11.

40. An isolated nucleic acid comprising a nucleotide sequence encoding the fragment of claim 23.

41. An isolated nucleic acid comprising a 5 nucleotide sequence encoding a protein, said protein comprising amino acid numbers 1-175 of the human Delta sequence depicted in Figure 11 (SEQ ID NO:18).

42. An isolated nucleic acid comprising a 10 nucleotide sequence encoding the protein of claim 17.

43. A recombinant cell containing the nucleic acid of claim 33.

15 44. A recombinant cell containing the nucleic acid of claim 39.

45. A recombinant cell containing the nucleic acid of claim 41.

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46. A method of producing a vertebrate Delta protein comprising growing a recombinant cell containing the nucleic acid of claim 33 such that the encoded vertebrate Delta protein is expressed by the cell, and recovering the 25 expressed Delta protein.

47. A method of producing a vertebrate Delta protein comprising growing a recombinant cell containing the nucleic acid of claim 41 such that the encoded Delta protein 30 is expressed by the cell, and recovering the expressed Delta protein.

48. A method of producing a protein comprising a fragment of a vertebrate Delta protein, which method 35 comprises growing a recombinant cell containing the nucleic acid of claim 39 such that the encoded protein is expressed by the cell, and recovering the expressed protein.

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49. The product of the process of claim 46.
50. The product of the process of claim 47.
- 5 51. The product of the process of claim 48.
52. A pharmaceutical composition comprising a therapeutically effective amount of a Delta protein; and a pharmaceutically acceptable carrier.
- 10 53. The composition of claim 52 in which the Delta protein is a human Delta protein.
54. A pharmaceutical composition comprising a  
15 therapeutically effective amount of the fragment of claim 11; and a pharmaceutically acceptable carrier.
55. A pharmaceutical composition comprising a therapeutically effective amount of the fragment of claim 23;  
20 and a pharmaceutically acceptable carrier.
56. A pharmaceutical composition comprising a therapeutically effective amount of a derivative or analog of a Delta protein, which derivative or analog is characterized  
25 by the ability to bind to a Notch protein or to a molecule comprising the epidermal growth factor-like repeats 11 and 12 of a Notch protein; and a pharmaceutically acceptable carrier.
- 30 57. A pharmaceutical composition comprising a therapeutically effective amount of the nucleic acid of claim 33; and a pharmaceutically acceptable carrier.
58. A pharmaceutical composition comprising a  
35 therapeutically effective amount of the nucleic acid of claim 35; and a pharmaceutically acceptable carrier.

59. A pharmaceutical composition comprising a therapeutically effective amount of the nucleic acid of claim 39; and a pharmaceutically acceptable carrier.

5 60. A pharmaceutical composition comprising a therapeutically effective amount of an antibody which binds to a Delta protein; and a pharmaceutically acceptable carrier.

10 61. A pharmaceutical composition comprising a therapeutically effective amount of a fragment or derivative of an antibody to a Delta protein containing the binding domain of the antibody; and a pharmaceutically acceptable carrier.

15 62. A method of treating or preventing a disease or disorder in a subject comprising administering to a subject in which such treatment or prevention is desired a therapeutically effective amount of a Delta protein or  
20 derivative thereof which is able to bind to a Notch protein.

63. The method according to claim 62 in which the disease or disorder is a malignancy characterized by increased Notch activity or increased expression of a Notch  
25 protein or of a Notch derivative capable of being bound by an anti-Notch antibody, relative to said Notch activity or expression in an analogous non-malignant sample.

64. The method according to claim 62 in which the  
30 disease or disorder is selected from the group consisting of cervical cancer, breast cancer, colon cancer, melanoma, seminoma, and lung cancer.

65. The method according to claim 62 in which the  
35 subject is a human.

66. A method of treating or preventing a disease or disorder in a subject comprising administering to a subject in which such treatment or prevention is desired a therapeutically effective amount of a molecule, in which the molecule is an oligonucleotide which (a) consists of at least six nucleotides; (b) comprises a sequence complementary to at least a portion of an RNA transcript of a *Delta* gene; and (c) is hybridizable to the RNA transcript.

67. A method of treating or preventing a disease or disorder in a subject comprising administering to a subject in which such treatment or prevention is desired an effective amount of the nucleic acid of claim 33 or 39.

68. A method of treating or preventing a disease or disorder in a subject comprising administering to a subject in which such treatment or prevention is desired an effective amount of the antibody of claim 30.

69. The method according to claim 62 in which the disease or disorder is a disease or disorder of the central nervous system.

70. An isolated oligonucleotide consisting of at least six nucleotides, and comprising a sequence complementary to at least a portion of an RNA transcript of a *Delta* gene, which oligonucleotide is hybridizable to the RNA transcript.

71. A pharmaceutical composition comprising the oligonucleotide of claim 70; and a pharmaceutically acceptable carrier.

72. A method of inhibiting the expression of a nucleic acid sequence encoding a *Delta* protein in a cell comprising providing the cell with an effective amount of the oligonucleotide of claim 70.



73. A method of diagnosing a disease or disorder characterized by an aberrant level of Notch-Delta protein binding activity in a patient, comprising measuring the ability of a Notch protein in a sample derived from the patient to bind to a Delta protein, in which an increase or decrease in the ability of the Notch protein to bind to the Delta protein, relative to the ability found in an analogous sample from a normal individual, indicates the presence of the disease or disorder in the patient.

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74. A method of diagnosing a disease or disorder characterized by an aberrant level of Delta protein in a patient, comprising measuring the level of Delta protein in a sample derived from the patient, in which an increase or decrease in the level of Delta protein, relative to the level of Delta protein found in an analogous sample from a normal individual, indicates the presence of the disease or disorder in the patient.

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75. A purified human protein which is encoded by a first nucleic acid that is hybridizable to a second nucleic acid having the nucleotide sequence depicted in Figure 12A (SEQ ID NO:33) or having an at least 50 nucleotide portion of said sequence.

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76. The fragment of claim 8 which is encoded by a first nucleic acid that is hybridizable to a second nucleic acid having the nucleotide sequence depicted in Figure 12A (SEQ ID NO:33) or having an at least 50 nucleotide portion of said sequence.

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77. The fragment of claim 10 which is encoded by a first nucleic acid that is hybridizable to a second nucleic acid having the nucleotide sequence depicted in Figure 12A (SEQ ID NO:33) or having an at least 50 nucleotide portion of said sequence.

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78. The fragment of claim 14 which is encoded by a first nucleic acid that is hybridizable to a second nucleic acid having the nucleotide sequence depicted in Figure 12A (SEQ ID NO:33) or having an at least 50 nucleotide portion of 5 said sequence.

79. The fragment of claim 25 which is encoded by a first nucleic acid that is hybridizable to a second nucleic acid having the nucleotide sequence depicted in Figure 12A 10 (SEQ ID NO:33) or having an at least 50 nucleotide portion of said sequence.

80. The fragment of claim 10 or 25, which is a fragment of SEQ ID NO:39.

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81. The fragment of claim 28 which is encoded by a first nucleic acid that is hybridizable to a second nucleic acid having the nucleotide sequence depicted in Figure 12A (SEQ ID NO:33) or having an at least 50 nucleotide portion of 20 said sequence.

82. An isolated nucleic acid comprising the nucleotide sequence depicted in Figure 12A (SEQ ID NO:33).

25 83. An isolated nucleic acid comprising a nucleotide sequence complementary to the nucleotide sequence depicted in Figure 12A (SEQ ID NO:33).

84. A purified protein comprising at least a 30 portion of a human Delta amino acid sequence, said portion selected from the group consisting of amino acid numbers 1-192 depicted in Figure 14 (SEQ ID NO:39), amino acid numbers 205-213 depicted in Figure 14 (SEQ ID NO:43), amino acid numbers 214-370 depicted in Figure 14 (SEQ ID NO:44), amino 35 acid numbers 371-382 depicted in Figure 14 (SEQ ID NO:45), amino acid numbers 394-418 depicted in Figure 14 (SEQ ID NO:49), amino acid numbers 419-428 depicted in Figure 14 (SEQ

ID NO:50), amino acid numbers 443-458 depicted in Figure 14 (SEQ ID NO:52), amino acid numbers 459-469 depicted in Figure 14 (SEQ ID NO:53), amino acid numbers 470-495 depicted in Figure 14 (SEQ ID NO:54), amino acid numbers 496-508 depicted in Figure 14 (SEQ ID NO:55), and amino acid numbers 516-519 depicted in Figure 14 (SEQ ID NO:59).

85. The protein of claim 84 which is encoded by a first nucleic acid that is hybridizable to a second nucleic acid having the nucleotide sequence depicted in Figure 12A (SEQ ID NO:33) or having an at least 50 nucleotide portion of said sequence.

86. A purified protein which is encoded by a first nucleic acid hybridizable under stringent conditions to a second nucleic acid having a nucleotide sequence comprising a sequence selected from the group consisting of nucleotide numbers 60-634 depicted in Figure 12B (SEQ ID NO:33), nucleotide numbers 746-772 depicted in Figure 12B (SEQ ID NO:33), nucleotide numbers 775-1245 depicted in Figure 12B (SEQ ID NO:33), nucleotide numbers 1249-1284 depicted in Figure 12B (SEQ ID NO:33), nucleotide numbers 1415-1489 depicted in Figure 12B (SEQ ID NO:33), nucleotide numbers 1493-1522 depicted in Figure 12B (SEQ ID NO:33), nucleotide numbers 1526-1567 depicted in Figure 12B (SEQ ID NO:33), nucleotide numbers 1570-1618 depicted in Figure 12B (SEQ ID NO:33), nucleotide numbers 1622-1653 depicted in Figure 12B (SEQ ID NO:33), nucleotide numbers 1658-1735 depicted in Figure 12B (SEQ ID NO:33), and nucleotide numbers 1739-1777 depicted in Figure 12B (SEQ ID NO:33).

87. The protein of claim 2 which comprises a portion of the human Delta amino acid sequence set forth in Figure 14, said portion selected from the group consisting of amino acid numbers 1-192 (SEQ ID NO:39), amino acid numbers 205-213 (SEQ ID NO:43), amino acid numbers 214-370 (SEQ ID NO:44), amino acid numbers 371-382 (SEQ ID NO:45), amino acid

numbers 394-418 (SEQ ID NO:49), amino acid numbers 419-428 (SEQ ID NO:50), amino acid numbers 443-458 (SEQ ID NO:52), amino acid numbers 459-469 (SEQ ID NO:53), amino acid numbers 470-495 (SEQ ID NO:54), amino acid numbers 496-508 (SEQ ID NO:55), and amino acid numbers 516-519 (SEQ ID NO:59).

88. The protein of claim 75 in which the first nucleic acid is hybridizable to the second nucleic acid under conditions of high stringency.

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89. The fragment of claim 76, 77 or 78 in which the first nucleic acid is hybridizable to the second nucleic acid under conditions of high stringency.

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90. An isolated nucleic acid hybridizable under conditions of high stringency to a nucleic acid having the nucleotide sequence depicted in Figure 12A (SEQ ID NO:33) or having an at least 50 nucleotide portion of said sequence.

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91. The nucleic acid of claim 90 which comprises a cDNA sequence hybridizable under conditions of high stringency to a nucleic acid having the nucleotide sequence depicted in Figure 12A (SEQ ID NO:33) or having an at least 50 nucleotide portion of said sequence.

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92. An isolated nucleic acid comprising a nucleotide sequence complementary to a cDNA sequence hybridizable under conditions of high stringency to a nucleic acid having the nucleotide sequence depicted in Figure 12A (SEQ ID NO:33) or having an at least 50 nucleotide portion of said sequence.

93. A purified human protein which is encoded by a first nucleic acid that is hybridizable to a second nucleic acid having the nucleotide sequence depicted in Figure 10 (SEQ ID NO:14) or having an at least 50 nucleotide portion of said sequence.

94. The fragment of claim 8 which is encoded by a first nucleic acid that is hybridizable to a second nucleic acid having the nucleotide sequence depicted in Figure 10 (SEQ ID NO:14) or having an at least 50 nucleotide portion of 5 said sequence.

95. An isolated nucleic acid hybridizable under conditions of high stringency to a nucleic acid having the nucleotide sequence depicted in Figure 10 (SEQ ID NO:14) or 10 having an at least 50 nucleotide portion of said sequence.

96. An isolated nucleic acid hybridizable under conditions of high stringency to a nucleic acid having the consensus nucleotide sequence depicted in Figure 13 (SEQ ID 15 NO:38) or having an at least 50 nucleotide portion of said sequence.

97. A purified protein encoded by a first nucleic acid hybridizable to a second nucleic acid having the 20 consensus nucleotide sequence depicted in Figure 13 (SEQ ID NO:38) or having an at least 50 nucleotide portion of said sequence.

98. An isolated nucleic acid comprising a 25 nucleotide sequence that is complementary to the nucleotide sequence of the nucleic acid of claim 92 or 96.

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